Remarks/Arguments

Restriction Requirement – Inventions of Groups 1-3

Claims 1-41 are pending in this application. Applicants were requested to elect, for examination in the present application, one of the following distinct inventions:

Group 1 (Claims 1-19): "as specifically drawn to the special technical feature of a method of inhibiting the proliferation of a target cell, comprising contacting the cell with a GPC5 antagonist of a GPC5 binding agent;

Group 2 (Claims 20-29 and 34-41): "as specifically drawn to the special technical feature of a method of determining the susceptibility of a cancer to treatment with a GPC5 antagonist or binding agent, comprising determining the presence, absence or level of expression of GPC5 and/or WT1 in a cell from said cancer; and

Group 3 (Claims 30-33): "as specifically drawn to the special technical feature of a method of screening for an agent capable of inhibiting proliferation of a target cell."

Applicants hereby elect the invention of Group 1, **with traverse**. Claims 1-19 encompass the elected invention.

Applicants submit that the present application provides the first hard evidence of a functional link between GPC5 and cancer cell proliferation, and shows for the first time that GPC5 represents a real therapeutic target. In view of this single general inventive concept, linking all claims pending, the restriction requirement is believed to be misplaced. Accordingly, all of claims 1-41 pending in this application should be examined together, as required by Rule 13.1 PCT.

The Examiner observes that "*the single general inventive concept which combines Groups 1-3 appears to be the nexus between GPC5 expression and cancer*" (Office Action, page 2, penultimate para.).

However, the single general inventive concept underlying the claims is not merely the finding that some cancers show overexpression of GPC5. Rather, it is the finding that GPC5 is actually involved in the proliferation of these cells and represents a genuine therapeutic target by which proliferation can be inhibited.

The Examiner goes on to say that "*Yu et al. ... teach that GPC5 is overexpressed in lymphoma cell lines and over-expression of GPC-5 contributes to teh [sic] development and/or progression of lymphomas and other tumors*".

This is a mis-quotation of the abstract of the paper, which actually says that "*over-expression of [GPC5] may contribute to development and/or progression of lymphomas and other tumours*". This is merely a speculative comment, and very far from being a positive disclosure that the GPC5 gene does contribute to cancer development.

The paper by Yu *et al.* shows that GPC5 is overexpressed in certain lymphoma cell lines which show chromosomal amplification of the 13q region. However, this alone says nothing about the 2 significance of that overexpression. As explained in the present application (discussing the paper by Yu *et al.*):

> "*Tumour cells are notoriously genetically unstable, being prone to acquiring genetic abnormalities, such as chromosomal amplifications, after transformation. It is therefore possible that the observed amplification [by Yu et al.] was acquired after transformation, or alternatively is simply not involved in the transformation process. Accordingly, there is no proof in the literature to date that GPC5 has any role in normal or abnormal cell proliferation.*" (Page 3, first paragraph.)

Thus, the unusual expression of GPC5 in these cells could have arisen after transformation. Even if it coincides with transformation, it could simply be a downstream consequence of more fundamental abnormalities within the cells, while having no effect in itself on cell proliferation.

Importantly, the paper contains no functional evidence that overexpression of GPC5 in these cell lines actually contributes to their abnormal proliferation, or that inhibition of GPC5 expression or activity would have any beneficial effect.

Thus, Yu *et al.* provides the skilled reader with no concrete teaching regarding the role of GPC5 in tumourigenesis or proliferation (even in cells which possess amplification of the 13q region), and provides no reason to believe that inhibition of GPC5 expression or activity would have a significant effect on cell proliferation.

Indeed, other authors had suggested that another gene in the 13q region, designated C13ORF25, was more likely than GPC5 to be functionally implicated in malignancy – see Ota *et al.*, Cancer Res. 64, 3087-3095 (2004), cited in the ISR and as ref. 33 in the present application.

By contrast, the present application provides the first demonstration that GPC5 is in fact linked to cancer cell proliferation, and that downregulation of GPC5 does indeed reduce the ability of transformed cells to form colonies. This is not restricted to cells with chromosomal amplification of 13q, since the inventors have shown that GPC5 is overexpressed in other cancer cell types which do not show chromosomal amplification.

Thus the present application provides the first hard evidence of a functional link between GPC5 and cancer cell proliferation, and shows for the first time that GPC5 represents a real therapeutic target. This therefore provides a single general inventive concept linking claim groups 1 to 3 as required by Rule 13.1 PCT.

Indeed, we note that the International Preliminary Report on Patentability received in connection with the corresponding PCT application considers the papers by Yu *et al.* and Ota *et al.* discussed above, and concludes that, at the filing date of the present application, the role of GPC5 in cancer was unclear and consequently that the skilled person "*would not be lead, at the relevant date of the present application, to the development of GPC5 inhibitors for cancer therapy with a reasonable expectation of success and without intervention of inventive skills*" (Item V(4)). All claims are acknowledged to be novel and inventive.

Thus, it must be concluded that Yu *et al.* does not disclose the single general inventive concept which links the claims. We therefore believe that all three claim groups are unified, and should be considered together in this application.

Restriction Requirement – Type of antagonist

The Examiner also considers that there is a lack of unity between the various types of GPC5 antagonists listed at page 3 of the Office Action.

Applicants elect antisense RNA (invention (c)), **with traverse**.

Claims 1-16 and 18-21 read on this invention. As explained above, the claims are unified because the prior art does not disclose that GPC5 is implicated in proliferation of cancer cells. Neither does the art disclose that inhibition of GPC5 expression or activity, using GPC5 antagonists, is capable of inhibiting cancer cell proliferation. It follows that the use of the various GPC5 antagonists disclosed in the application to inhibit cancer cell proliferation constitutes a single unified invention.

As the Examiner acknowledges, the various antagonists listed do not all "*share substantial structural similarities*", but do "*have a common utility*". This common utility, and its use to inhibit cell proliferation, constitutes a special technical feature per Rule 13.2 PCT. Therefore the claims are unified insofar as they relate to these various antagonists.

Even if the Examiner rejects this reasoning, three of the five listed types of antagonist do indeed share "*substantial structural similarity*". Although working by slightly different mechanisms, antisense RNA, dsRNA/RNAi and ribozymes are all RNA molecules which exert an antagonist activity on GPC5 expression as a result of sharing considerable sequence identity or complementarity with the mRNA of GPC5, as specified in claim 14. Thus, even if these RNA-based antagonists are considered to lack unity with protein-based antagonists (such as antibodies and binding peptides) we believe that they should be considered as one group.

Election of Species Requirement

Applicants were requested to elect one of the species listed on pages 4-5 of the Office Action.

Applicants hereby elect the species of breast cancer (species (e)).

Claims 1-21 read on this species.

The Commissioner is hereby authorized charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account **50-4634** (Attorney Docket No. **124263-186545** (**MWB-0004**).

Respectfully submitted,

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